Bayer

Bayer AG

Geschäftsbereich Pharma
Qualitätssicherung
Qualitätskontrolle Wirkstoffe

PH-QA-QW
Geb. 302
D-42096 Wuppertal

Telefon: (0202) 36-2233
Telefax: (0202) 36-2633

Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, rm 1061
Rockville
MD 20852

USA

Wuppertal, 30.03.1999
La039901.doc

**Subject: Docket No. 98D-0994**

Dear Sir or Madam

Please find enclosed the Bayer AG comments on:

Draft Guidance for Industrie on BACPAC I: Intermediates in Drug Substance Synthesis

Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Dokumentation (Docket No. 98D-0994)

Yours sincerely

Dr. G. Maldener
Head of Operations Drug Substance

Enclosures

98D-0994

C22

3670 '99 MAR 31 P3:25

3130092

BAYER AG COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY ON BACPAC I [Docket No. 98D-0994]

Bayer welcomes the Draft Guidance for Bulk Actives Postapproval Changes in the BACPAC I document.
Experience has shown that the current regulations are too strict, complex and not flexible enough to allow the API-producer to adopt his products to scientific and technical progress and also to economical needs. On the other hand the authorities of the different countries must be sure that the production of API's is always in compliance with cGMP and the marketing authorisation.
First we think that this Draft Guidance is on the right lines and shows quite a good balance between these two point of views. It is very important that in this draft guidance the FDA clearly expresses the fact that there is a great difference between the dosage form manufacturing and the API production. Within the API production there are also differences between the production of the intermediates including the final intermediate and the production of the API itself. As expressed in the document the API's and their intermediates are normally well characterized substances with a well defined quality which is fixed in a specification. This specification is the base for the necessary quality of the API as laid down in the marketing authorisation. On the other hand it is very clear that this quality is build into the substance by a well defined process with fixed process parameters which are also laid down in the marketing authorisation. But it is important to remember that the only reason for a fixed specific process is to get reliably the necessary quality of the product. This means that we have a clear measurement for the effectiveness of a defined process and therefore also for changes in this process. Last but not least is this quality assured only in a cGMP controlled environment with all the necessary rules and documentation. These facts can also be systematically used for the classification and the handling of changes in the API production and we are glad to see that this is done in the BACPAC I document perhaps at some points not with the desired consequence.
A meaningful classification of changes could be made as follows:

1. Changes which affect only the GMP-System or the environment e.g. site changes, equipment changes and changes of the scale of production (**class 1**).
2. Changes of information related to the process itself e.g. process parameters like temperature and pressure, change in solvents and changes in the route of synthesis including the final intermediate (**class 2**).
3. Changes in the specification of all substances (**class 3**) divided in two groups
   - all substances up to the final intermediate (**group 1**)
   - the final intermediate (**group 2**)

According to this classification we would like to see that the draft guidance would be revised in the following manner:

1. Within BACPAC I there should be a strict separation between first all changes witch are only *GMP related* (**class 1**) and second the changes witch affect only *technical information* in the dossier with no influence on the quality of the API (**class 2**) and third the changes in specifications (**class 3**).

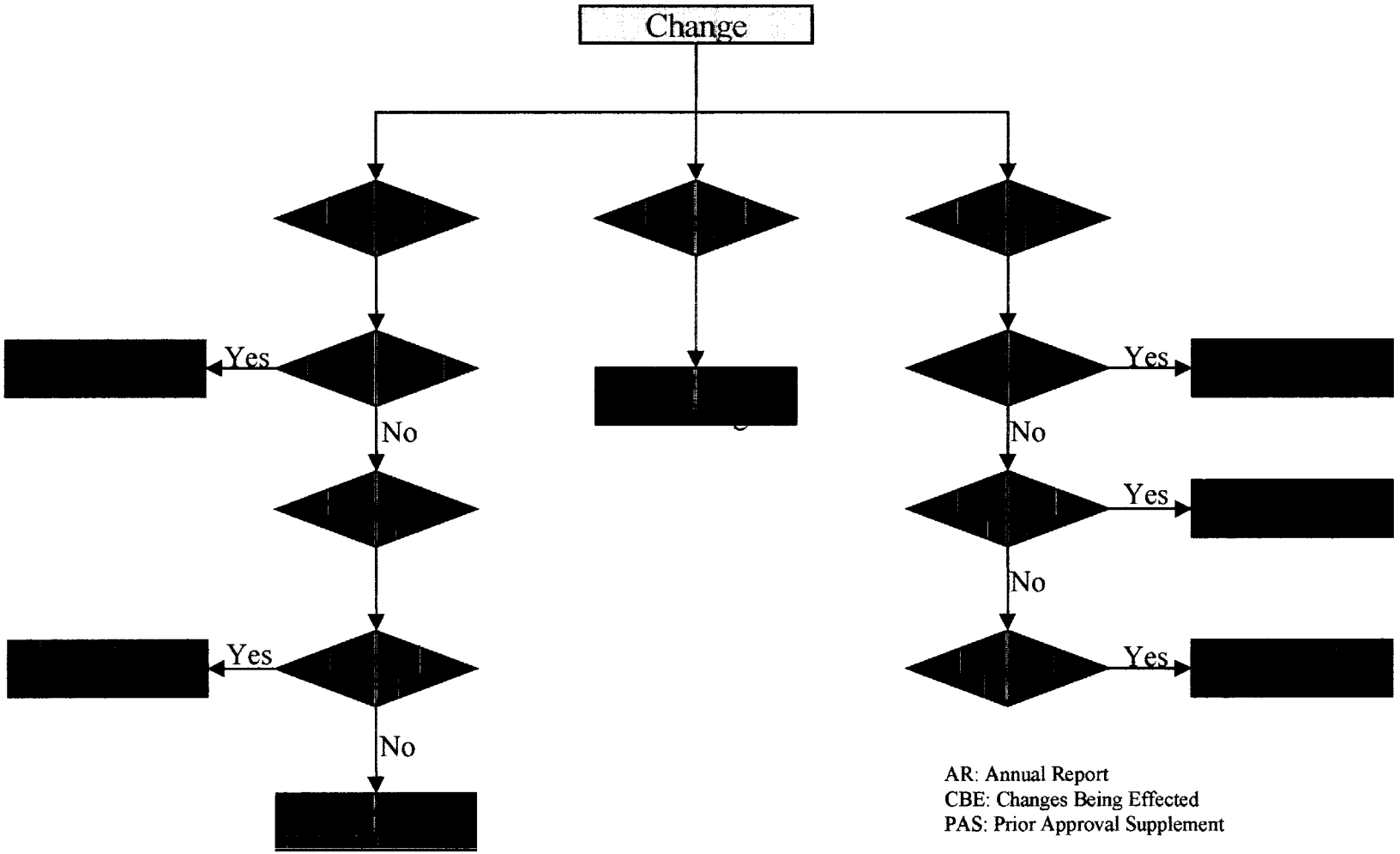
2. If the company could proof that the change leads to the same quality of the **final intermediate** -as defined in the document- (**case 1**) there should be never the necessity to get a prior approval before implementing the change and only if the route of synthesis of the final intermediate is changed or it is bought from a not approved supplier (**case 2**) there is the necessity for a CBE. If the change leads to a final intermediate with a different quality but within the approved specification and the API has the same quality the company will have to file a CBE (**case 3**).

3. All changes of specifications except from the final intermediate (**group 1**) which do not influence the specification of the final intermediate should be filed in the annual report. A change in the specification of the final intermediate (**group 2**) has to be filed as a CBE if the company can proof equivalence of the API

If these general principles are accepted this would result in a very simple decision-tree for each change in the scope of BACPAC I (Attachment A).

Attachment A

# Decision-tree for BACPAC I



TNT

806192305

COLLI: 01/01

AIR

2

ORIGIN

DUS 30.03.99

21/62390

99089 18:46

PMX FIS 990322

TNT REF:

EURO DESTINATION AIRPORT:

VIA:

EXPRESS DOCUMENTS

DESTINATION:

DELIVERY:

ROCKVILLE

B --

20852

BWI

USA UNITED STATES

**TELEPHONE NO:**

**SENDING DEPOT:**

**NUMBER OF PIECES:**

**WEIGHT:**

**CONSIGNMENT NOTE NUMBER:**

**DESTINATION DEPOT:**

CDA VLAGE

Sender TNT Account: 42231
BAYER AG
FRIEDRICH-EBERT-STR. 217 333
WUPPERTAL
42117
NOR
GERMANY
Contact: ZL VKB EXPEDITION
Tel: 0202- 362287

**TNT Express Worldwide**

*806192305*

Sender Ref: 21/62390

Delivery Address
FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE,RM 1061
DOCKETS MANAGEMENT BRANCH
ROCKVILLE
20852
MD
USA

Description Of Goods: Documents

Pickup Date: 30 MAR 99

Dimensions:

Special Delivery Instructions

Service & Options
(82) DOCUMENTS

No Of Pieces
1 of 1

Consignment Weight
0.100kgs

TNT EXPRESS WORLDWIDE'S LIABILITY FOR LOSS, DAMAGE AND DELAY IS LIMITED BY THE CMR CONVENTION OR THE WARSAW CONVENTION WHICHEVER IS APPLICABLE. THE SENDER AGREES THAT THE GENERAL CONDITIONS, ACCESSIBLE VIA THE PARTNERSHIP FUNCTION 'TERMS', ARE ACCEPTABLE AND GOVERN THIS CONTRACT. IF NO SERVICE OR BILLING OPTION IS SELECTED THE FASTEST AVAILABLE SERVICE WILL BE CHARGED TO THE SENDER.